detected using standard assays. When unmetabolized terfenadine accumulates, however, it can induce a quinidine-like delay in cardiac repolarization that increases the risk of ventricular arrhythmias such as torsades de pointes. Consequently, any increase in the serum concentration of unmetabolized terfenadine increases the risk of QT prolongation and, therefore, serious cardiac arrhythmias.

Several clinical situations can lead to increased levels of unmetabolized terfenadine. In cases of acute overdose (as low as 360 mg) or in patients with impaired liver function, the hepatic metabolism of terfenadine may be overwhelmed. In addition, several medications can impair the metabolism of terfenadine. Because ketoconazole is an imidazole antifungal agent with potent inhibitory effects on cytochrome P450, unmetabolized terfenadine is detectable when these drugs are used concomitantly. In six healthy volunteers, the concomitant use of terfenadine and ketoconazole resulted in substantial increases in unmetabolized terfenadine and lengthening of the QT interval in all six subjects. The related compound, itraconazole, demonstrates the same inhibitory effect. By a similar mechanism, erythromycin blocks the metabolism of terfenadine, although probably to a somewhat lesser degree than does ketoconazole. Whereas other macrolide antibiotics such as troleandomycin and clarithromycin produce similar inhibitory effects, azithromycin may not undergo P450 oxidation and does not appear to interact with terfenadine in preliminary studies. Because cyclosporin is metabolized by the same hepatic cytochrome as terfenadine, agents that have been shown to inhibit cyclosporin metabolism may exhibit similar effects on terfenadine, including metronidazole, verapamil, diltiazem, and grapefruit juice. Finally, caution should be used when administering terfenadine concomitantly with agents that prolong the QT interval such as type IA antiarrhythmics (quinidine sulfate, procainamide hydrochloride, and disopyramide phosphate), tricyclic antidepressants, sotalol hydrochloride, haloperidol (a structural analogue of terfenadine), thioridazine, probucol, cisapride, and pentamidine.

Astemizole is metabolized by the same cytochrome enzyme, and unmetabolized astemizole also demonstrates QT prolongation when serum concentrations are increased. Cases of adverse cardiovascular events have been reported when astemizole has been taken with erythromycin, ketoconazole, or itraconazole or at higher than the recommended dose. In general, any of the described conditions related to terfenadine toxicity should be considered for astemizole as well.

Loratadine (Claritin, Schering) and cetirizine hydrochloride (not yet approved by the Food and Drug Administration) are newer nonsedating antihistamines that have not shown cardiotoxic effects in preliminary studies. Although ketoconazole inhibits the metabolism of loratadine, no electrocardiographic effects were noted in 24 patients receiving concomitant therapy. Studies in humans and animals confirm the lack of cardiac effects in elevated dosages, and no ventricular arrhythmias associated with its use have been reported to date. Cetirizine hydrochloride also appears to be free of cardiotoxic effects in dosages as much as six times the recommended dose. Although these studies are preliminary, they suggest that these newer antihistamines may be safe alternatives when terfenadine or astemizole therapy is contraindicated.

Under certain circumstances, terfenadine and astemizole can induce life-threatening cardiac arrhythmias. The use of these agents should be avoided in patients with hepatic dysfunction and in patients receiving drugs that may inhibit their metabolism or prolong the QT interval, and these drugs should not be taken in excessive dosages. In addition, primary care and emergency physicians must consider these interactions in the examination of patients presenting with syncope or cardiac arrhythmias.

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Role of Glucocorticosteroids in Treatment of Acute Spinal Cord Injury

THE ROLE OF GLUCOCORTICOSTEROIDS in the treatment of acute spinal cord injury has long been controversial. The mechanisms through which steroids exert their effects following spinal cord injury are still unknown. The leading theory is that steroids inhibit post-spinal cord injury lipid peroxidation and enhance recovery by inhibiting the injury-induced degenerative cascade that follows. Animal models of spinal cord injury treated with steroids in the early 1970s served as the basis for the National Acute Spinal Cord Injury Study (NASCIS I), published in 1985. This landmark study found no improvement in neurologic recovery in patients with acute spinal cord injury after the administration of methylprednisolone sodium succinate. Findings in animals suggesting that a higher dose of methylprednisolone may be beneficial led to NASCIS II, published in 1990.

In NASCIS II, patients with acute blunt spinal cord injury were randomly assigned to receive either methylprednisolone (30 mg per kg of body weight in an intravenous bolus, then 5.4 mg per kg per hour for 23 hours), naloxone, or placebo in a double-blind, prospective, multicenter clinical trial. Analysis of the entire study population did not show any statistically significant difference in the study arms. Subgroup stratification, however, found that the group receiving methylprednisolone in less than eight hours after injury showed significant

improvement in the neurologic score. The authors went on to conclude that these improved neurologic scores were "significant improvements in motor function and sensation." This resulted in the widespread use of high doses of methylprednisolone for acute spinal cord injury. Misinterpretation of this complex study has led to much confusion regarding eligibility criteria, benefits, and risks for patients with spinal cord injury who receive high doses of methylprednisolone.

NASCIS II relied on subgroup stratification to reveal any significant benefit of steroid use in acute spinal cord injury. Fundamental methodologic problems exist with subgroup stratification that is not followed by prospective validation of the results. Although subgroup stratification found high-dose steroids given within eight hours of injury improved neurologic scores, high-dose steroids given after eight hours actually caused significant worsening of neurologic scores. In addition, the authors themselves conclude that they were not able to translate the improvements in neurologic score into any improvement of functional status—quadriplegia improving to quadriparesis or paraplegia, and the like. NASCIS II excluded patients with serious coexisting life-threatening injuries and patients with spinal cord injury due to gunshot wounds; therefore, no conclusions regarding steroid use in these patients may be drawn. Finally, the safety profile of high-dose steroids remains in doubt. Whereas NASCIS I concluded that the use of steroids was associated with a statistically higher rate of infection, NASCIS II did not. A plausible explanation would be that NASCIS II lacked sufficient power to detect a significant difference in infection rates.

High-dose methylprednisolone—30 mg per kg of body weight given intravenously over 15 minutes, followed by a 45-minute rest period, then 5.4 mg per kg per hour for 23 hours—does appear to improve the neurologic state of patients with acute spinal cord injury if given within eight hours of injury. Based on available literature, if a patient is without life-threatening comorbidity and is suffering from blunt trauma-related spinal cord injury, administering high-dose methylprednisolone appears prudent. Whether this practice has a solid scientific basis awaits prospective validation of the results found in NASCIS II. The safety profile and how "improved neurologic scores" translate into functional neurologic recovery remain in doubt. Based on the current literature, the administration of high-dose methylprednisolone is not indicated and may be harmful if more than eight hours have elapsed since injury. There is no published scientific evidence to conclude that a patient with penetrating trauma-related spinal cord injury or with life-threatening comorbidity benefits from steroid therapy. Further studies on the effectiveness and safety profile of high-dose methylprednisolone are needed to clarify its role in acute spinal cord injury.

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